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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHIBUYA, MARK LANCE	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,296	KIESSLING ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-157* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,17-23,28-30,41,42,59,60,62,64,66,68,71-74,81-86,90-92,94,95,140-155 and 157* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/10/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-0-0

DETAILED ACTION

1. Claims 1-157 are pending. Claims 4-16, 24-27, 31-40, 43-58, 61, 63, 65, 67, 69, 70, 75-80, 87-89, 93, 96-139 and 156 are withdrawn from consideration. Claims 1-3, 17-23, 28-30, 41, 42, 59, 60, 62, 64, 66, 68, 71-74, 81-86, 90-92, 94, 95, 140-155 and 157 are examined.

Election/Restrictions

2. The requirement for election/restrictions, as set forth in the previous Office action, is maintained.

3. Claims 4-16, 24-27, 31-40, 43-58, 61, 63, 65, 67, 69, 70, 75-80, 87-89, 93, 96-139 and 156 remain withdrawn from consideration as non-elected and withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Information Disclosure Statement

4. The IDS, entered 10/10/2002, has been considered.

Specification

5. Applicant's representative, in the Reply to the previous Office action, at p. 13, declares that the amendment to the specification consists of the same material

incorporated by reference from Ranaschi et al. The declarant states that the declaration made within the Reply is sufficient and that a separate paper is not required.

Upon further consideration, the requirement for affidavit or declaration in order to incorporate essential material is withdrawn. Upon further consideration, the subject matter is not deemed essential, as it is not claimed, and is not necessary to overcome any rejection. Furthermore, the sentence added at p. 41 of the substitute specification, is not considered to be new matter, as the sentence forms the title of reference [67], which is found at p. 56 of the substitute specification, entered 8/1/2001, and was in the specification as filed.

Withdrawn Claim Rejections

6. The rejection of claims 1-3, 17-23, 28-30, 41, 42, 59, 60, 62, 64, 66, 68, 71-74, 81-86, 90-92, 94, 95, 140-146, and 148-155 and 157 under 35 U.S.C. § 112, second paragraph, is withdrawn in view of applicant's arguments and amendments to the claims.

7. The rejection of claims 1, 2, 17, 18 and 19 under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO 98/46270, (reference 4, IDS filed 10/10/2002) and Shea et al., Biophysical Journal, 1997, vol. 73, pp. 2949-2959, is withdrawn. Upon further consideration, the examiner finds that the reference of Whitesides et al., anticipates claims 1, 2, 17, 18 and 19, (but see below prior art rejections).

8. Upon further consideration, the rejection of claims 1, 62, 64, 66, 82, 83, and 84 under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO 98/46270 (reference 4, IDS filed 10/10/2002), Kiessling et al., US 6,291,616 (reference 1, IDS filed 10/10/2002), and Painter et al., Journal of Cell Biology, 1987, vol. 105, pp. 2959-2971 is withdrawn by the examiner, (but see below prior art rejections).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 17-23, 28-30, 41, 42, 59, 60, 62, 64, 66, 68, 71-74, 81-86, 90-92, 94, 95, 140-143, 151-155 and 157 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for lack of written description.

The claims are broadly drawn to methods for inducing a biological response in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements (see claim 1). The specification (at p. 27, lines 18-20) contemplates, methods wherein the multivalent ligands of the instant invention are useful "for controlling or modulating the effect of chemical signals in a biological

system." The specification, at p. 27, lines 19-23, states that the instant disclosure exemplifies application of "multivalent ligands to bacterial and eukaryotic chemotaxis, to migration of leukocytes (particularly neutrophils), to immune responses of B-cells and T-cells, to cell aggregation, and to signaling of apoptosis." Actual working embodiments (specification at p. 45, line 21-p. 50, line 27 and pp. 60-64, Scheme 1-Scheme 5) involve saccharide ligands for chemotaxis in *E. coli* and concanavalin A-mediated agglutination in Jurkat T cells and erythrocytes and PC12 cell cytotoxicity experiments.

Vas-Cath Inc. v. Mahurkar, 19 USPQ 2d 1111, 1117, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

To provide adequate written description and to provide evidence of possession of a claimed genus, the specification must provide a representative number of species. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus and describe sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and / or chemical properties, functional characteristics, structure / function correlation, methods of making the claimed product, and combinations thereof.

The broad genus of methods inducing a biological responses using multivalent ligands admits to substantial variation that would include virtually any biological response. The specification exemplifies five general categories (chemotaxis, leukocyte migration, immune response, cell aggregation and apoptosis) and provides working examples of as few as two multivalent ligands (a saccharide and concanavalin A). The examiner respectfully submits that the examples are not so comprehensive as to be representative of the full scope of the claimed genus. Furthermore, the rejected claims recite little molecular structure or identity for the receptors, signal recognition elements, or molecular scaffold. Accordingly, the specification does not provide adequate written description of the claimed genus of methods inducing biological responses, comprising receptors, ligands, and molecular scaffolds.

The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of all multivalent ligands that bind to any receptor to induce any biological response, and given the few actual examples provided and the unpredictability of the ligand-receptor and medicinal drug art, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making and using multivalent ligands. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The multivalent ligands themselves are required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, at 1483 (finding claims directed to

mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the *bovine* sequence).

Therefore, only the methods comprising specific multivalent ligands that bind to cellular receptors to induce chemotaxis or agglutination, as taught by the instant specification, but not the full breadth of the claim, meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 1, 2, 3, 17, 19, 21, 22, 30, 59, 60, 62, 68, 81, 82, 85, 86, 90, 91, 95, 142, 143, 144, are rejected under 35 U.S.C. § 102(a) as being anticipated by Gordon et al., (Chemistry & Biology, vol. 7:9-16, 2000). This rejection maintains the reasons of record set forth in the previous Office action, mailed 6/3/2004, and is extended to claims 2, 3, 17, 19, 21, 22, 30, 59, 60, 62, 68, 91, 95, 142, 143 and 144.

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements bonded to molecular scaffold and

wherein the signal recognition elements are recognized by at least one of the receptors, and variations thereof.

Gordon throughout the publication and at the abstract, p. 9, para 4-p. 10, para 2, teaches, teaches using ring-opening metathesis polymerization (ROMP) to generate to form multivalent arrays that include multivalent ligands for binding to cell surface receptors; teaches at Figures 3-5, polymers of the general formula of claims 82, 91 (e.g., m=0 and n=2 or more) and 144; at p. 13, para 2 and 3, teaches multivalent ligands coupled to a fluorescent reporter group that is fluoresce in, where the signal recognition element binds to L-selectin, which acts to recruit white cells to sites of tissue damage, and so acts as a guide to cells, i.e., chemoattractant, as demonstrated on human T-cells (Jurkat cells).

Response to Arguments

Applicant, in the reply to the previous Office action, argues that the reference of Gordon, "while teaching that certain multivalent ligands bind to L-selectin, does not demonstrate that this binding effects any biological response. Gordon does not show that binding of a multivalent ligand to L-selecting 'recuits cells to sites of tissue damage.'" Reply at p. 17. Applicant argues that the rejected claims are all directed to methods of inducing a biological response. "Since Gordon does not demonstrate induction of such response, it does not provide all of the elements of the claims and as such does not anticipate the claims." Reply at p. 17. Applicant also argues that Gordon does not teach an SRE that is a peptide (as in claim 83), a chemoattractant (as in claim 85) or an epitope (as in claim 86).

The rejection of claim 83 under 35 USC 102 (b) over Gordon is withdrawn, in view of applicant's arguments.

Applicant's arguments filed 1/11/2005 have been fully considered but they are not persuasive. Gordon at p. 9, para 2 and 3 teaches that attachment of assemblage of biologically active multivalent ligands, and that multivalent recognition events have importance in biology. Gordon at p. 10 teaches ligands that target selectins and that selectins are cell-surface proteins that facilitate the recruitment of leukocytes to sites of inflammation, that selectins have been inhibited with multivalent ligands, and that multivalent ligands have greater potency than monovalent counterparts. Gordon at p. 10-p. 11, bridging paragraph, and p. 13, para 4, cites references showing that L-selectin recruitment of white blood cells to cites of inflammation was known in the art and teaches a neoglycopolymer bearing a 3,6-disulfogalactose epitope (as in claim 86), such as compound **11a** and its reporter derivative, compound **16**, (see also Fig. 5) as multivalent ligands of L-selectin. Also, the instant Specification states: "Most non-self proteins and many carbohydrates are antigens, so epitopes, without limitation, proteins fragments (e.g., peptides) and carbohydrate fragments (e.g., saccharides and oligosaccharides)." Specification at p. 15, line 26-29. Therefore, the saccharide ligands taught by Gordon are epitopes. Gordon at pp. 13-14, bridging paragraph, states the multivalent ligands taught have biological activities that range from their function as effective inhibitors of the selectins to molecules that promote L-selectin downregulation from the cell surface. Gordon at p. 13, para 3-4, teach neoglycopolymer reporter ligand **16** as binding Jurkat cells, and teaches that these neoglycopolymers inhibit L-selectin-

mediated cell rolling. Gordon at p. 10, para 2 and p. 11, para 1, teaches that selectins recruit leukocytes to sites of inflammation, reading on chemoattraction (as in claim 85) and that selectins are mucin-like proteins that present multiple copies of anionic saccharide epitopes, and that neoglycopolymers, such as compound **11**, mimic mucins, and inhibit selectins by adopting structures similar to selectins, so that, absent evidence to the contrary, the multivalent ligands comprising compounds **11** and **16**, further mimic the chemoattractant properties of selectins.

Furthermore, in response to applicant's argument that the methods of inducing a biological response of the claimed invention are not taught by the reference of Gordon, applicant has not indicated how the multivalent ligand of claimed invention results in a structural difference from the multivalent ligand as taught by Gordon. Absent evidence to the contrary, the methods and the multivalent ligands taught by Gordon are capable of performing the intended use, and so meet the limitations of the rejected claims. Also, the term "biological response" is very broad and the specification and the claims do not provide a specific, limiting definition for the term.

11. Claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 82, 83, 90-92, 94, 95 140-143, 151, 154, 155, 157 are rejected under 35 U.S.C. § 102(b) as being anticipated by Whitesides et al., WO 98/46270 (reference 4, IDS filed 10/10/2002). This rejection maintains the reasons of record set forth in the previous Office action, mailed 6/3/2004, and has been extended to claims 18, 19, 82, 83, 90-92, 94, 95, and 141.

Whitesides, throughout the publication and at p. 3, lines 11-24, p. 7, lines 24-31, p. 14, lines 1-9, p. 15, lines 20-31, teaches multivalent ligands on a polymeric backbone of the form $Y-(A)_n$, where Y is a framework, A is a functional group, and n is an integer greater than 10, 50 or more, or about 100 or more and wherein the functional group that is a signal recognition is covalently bonded to the framework that is a molecular scaffold, such as a liposome; teaches at p. 32, lines 7-13, polyvalent presenters that include Sialyl Le^x that bind leukocyte receptor sites including integrins and selectins and are elements involved in signal recognition, inducing intracellular and intercellular responses; teaches at p. 60, line 26-p.61, line 20 modulation of cell-cell interactions by polyvalent presenters, (which include multivalent ligands), whereby numerous cell-cell interactions can be promoted or inhibited, such as neutrophil attachment to endothelial cells during inflammation; teaches at Table 2, p. 62, line 4-p. 63, line 7, cell-cell interactions that comprise neutrophil, endothelial cells, T–cells, and the release of platelet granules; at p. 87, lines 3-18, teaches cytokine production by replacing a stimulator cell in a cell-cell interaction that normally leads to cytokine secretion, e.g., using L-selectin ligands to simulate monocytes and macrophages to produce tumor necrosis factor; teaches at p. 96, line 1-p. 99 line 16, *in vitro* assays; at p. 97, line 31- p. 99, line 16, teaches cross-linking multivalent receptors on the cell by agglutinins to prevent the biological response of viral binding to the cell surface.

Whitesides, for example, at p. 118-120, Example 5, p. 141, Figure 11, teach methods for facilitating the treatment of influenza by inhibiting influenza-mediated hemagglutination comprising multivalent ligands of the formulas of claims 82 and 91

(where m=0 and n=2 or more), where SRE is NeuAc connected by a linker to a backbone repeating unit that is acyclic, R4-R6 are organic groups, and Z is H or an organic group.

Whitesides, at p. 93, line 18-p. 94, 12, teach an intracellular signal transduction mechanism triggered by activation of certain G-protein coupled receptors that that mediates intracellular signal transduction (as in claims 18 and 19) and results in a reaction of the acrosomal exocytosis of sperm.

Response to Arguments

Applicant, at pp. 18-19, bridging paragraph, argues that "although there is much discussion in the reference. . . concerning biological responses, the Whitesides et al. reference does not demonstrate induction of a biological response. Whitesides et al. demonstrate binding by ligands and inhibition of binding. . . . The Office Action characterizes "viral-binding " as a biological response. Applicants disagree with this characterization. Viral binding is a binding event not a biological response. . . . Thus this reference does not teach all of the elements of Applicant's claimed invention and should not be considered to anticipate these claims." The term "biological response" is very broad and the specification and the claims do not provide a specific, limiting definition for the term.

Applicant argues further that Whitesides does not teach a biological response in an epithelial, endothelial, immune system, lymphocytic, leukocytic, neutrophilic B or T cell, as in claims 20-23 or 30. Applicant argues that Whitesides does not teach a multivalent ligand that functions for the initiation or release of an intracellular signal by a

cell, and does not teach a multivalent ligand that releases a chemical signal which is a naturally-occurring drug, a hormone, an antigen, a growth factor, a cytokine, a protein, a peptide, a derivatized peptide, a saccharide, derivatized saccharide, nucleic acid, cell nutrient or epitope, as in claims 28, 29, 151, 154, and 155. Applicant argues that Whitesides does not teach a multivalent ligand that functions to reorganizes receptors on the surface of a cell to modulate a biological response, as in claims 41 and 42. Applicant argues that the Office action does not point to any specific passage in the Whitesides et al. reference that teaches the use of a multivalent ligand bound to a solid support, as in claim 140.

Applicant's arguments filed 1/11/2005 have been fully considered but they are not persuasive.

Applicant's representative concludes that "viral binding" is not a biological response, but provides no actual evidence that this is case. The binding of viruses is biological response, for it is well known that viruses attach to cells to infect them, and that antibodies bind to viruses to neutralize them. Whitesides at p. 69, line 1-4. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145.

Furthermore, Whitesides at p. 4, lines 7-17, teach, for example, methods for treating a disease or condition using polyvalent ligands, which read on effecting a

biological response; or for treating a number of disease, Whitesides at p. 94, line 22-p. 95, line 9.

Whitesides, for example at p. 61, states that polyvalent presenters (reading on multivalent ligands) can be used to modulate cell-cell interactions and that numerous biological processes require cell-cell interaction that can be promoted or inhibited, and at Table 2, p. 62, list cells whose biological response may be so affected, said cells including neutrophils, endothelial, and cells, as in claims 20-23 and 30. Whitesides, for example at p. 94, lines 7-12, teach an intracellular signal transduction mechanism triggered by activation of certain G-protein coupled receptors that results in a reaction of the acrosome of sperm, and at p. 94, lines 1-21, teach using multivalent GlcNac ligands to induce acrosomal exocytosis of mouse sperm, that involves an intracellular signal, as in claims 28, 29, 154 and 155. Whitesides, for example at p. 87, lines 3-18, teach the modulated release of cytokines by polyvalent ligands, as in claim 155. Whitesides, for example at p. 94, lines 7-8, teach reorganization of cell surface receptors involved in fertilization, which reads on modulating a biological response, or at p. 97, line 31-p.99, line 15, teaches crossing linking multivalent receptors to prevent viral binding to cell surfaces, as in claims 41 and 42. Whitesides at p. 36, lines 9-22, teach polyvalent ligands on solid supports, such as beads, that are useful in screening for a adhesion, or adhesion resulting in, for example, infection, cell death, cell proliferation, morphological change, etc., as in claim 140. Therefore, Whitesides et al., throughout the patent teach the claimed invention, as set forth above and in the previous Office action.

12. Claims 1, 81, 82, 83, 85, and 90 are rejected under 35 U.S.C. § 102(e) as being anticipated by Kiessling et al., US 6,291,616, (reference 1, IDS filed 10/10/2002).

Response to Arguments

Applicant, at pp. 20-21, bridging paragraph, argues that Kiessling teaches any multivalent ligand that induces a biological response, as required by the claims. Therefore, applicant argues, Kiessling does not teach the claimed method and does not anticipate the claims.

Applicant's arguments filed 1/11/2005 have been fully considered but they are not persuasive.

Kiessling at col. teaches coupling an amine-containing saccharide moiety to yield a 3,6-disulfogalactose derivative to form neoglycopolymers. Kiessling at col. 13, lines 51-60, teaches that L-selectin facilitates the recruitment of white blood to sites of tissue damage and that these neoglycopolymers inhibit selectin function by binding to L-selectin on the cell surface. Kiessling at col. 14, lines 5-19, teach that these neoglycopolymers bind to Jurkat cells, and at col. 14, lines 20-27, state: "Moreover, further microscopy studies suggest that the significant biological activities of these glycoprotein mimics are mediated through multivalent contacts." Thus Kiessling teach methods comprising glycopolymer multivalent ligands that induce a biological response, as in the claimed invention. The term "biological response" is very broad and the specification and the claims do not provide a specific, limiting definition for the term

13. Claims 1-3, 59, 60, 62, 64, 68, 74, 81, 82, 83, 90, 91, 92, 144, and 157 are rejected under 35 U.S.C. 102(a) as being anticipated by Arimoto et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11).

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements bonded to molecular scaffold and wherein the signal recognition elements are recognized by at least one of the receptors, and variations thereof.

Arimoto et al., throughout the publication and Figures and Scheme 1, teach methods for inducing antibacterial activity by introducing a multivalent ligand comprising a plurality of vancomycin residues, reading on signal recognition elements bonded to a ROMP-derived molecular scaffold of the formula of claim 82, that binds to D-Ala-D-Ala residue of the pentapeptide terminal of biosynthetic intermediates, which, absent evidence to the contrary, reads on a receptor of bacteria. Arimoto teaches at Scheme 1, polymers of the general formula of claims 82, 91 (where m=0 and n=2 or more) and 144.

14. Claims 1-3, 17, 28, 29, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90, 91, 142, 144, 152 and 157 are rejected under 35 U.S.C. 102(b) as being anticipated by Kanai et al., J. Am. Chem. Soc, 1997, Vol. 119 (41), pp. 1361-1362, (IDS filed 10/10/2002, ref. 45).

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand

comprising a plurality of signal recognition elements bonded to molecular scaffold and wherein the signal recognition elements are recognized by at least one of the receptors, and variations thereof.

Kanai et al., throughout the publication, teach methods for inducing interference with erythrocyte agglutination mediated by the carbohydrate-binding protein concanavalin A by introducing multivalent ligands which posses a plurality of saccharide residues, which read on a plurality of signal recognition elements, that are covalently bonded (as in claim 74) to a ROMP-derived scaffold of the formula in claim 82. Kanai, at Table 1, teach more than 100 repeating units in the neoglycopolymer, as in claims 71-73. Kanai et al. teaches at Figure 1, polymers of the general formula of claims 82, 91 (where m=0 and n=2 or more) and 144. Concanavalin A induces an intracellular signal by increasing Ca^{2+} concentration in the cell, as evidenced by Ramaschi et al., (IDS filed 10/10/2002, ref. No. 76).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90-92, 94, 95, 140-143, 144, **148**, **149**, 151, 154, 155, 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO 98/46270 (reference 4, IDS filed 10/10/2002); and Arimoto et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11).

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal recognition elements are bonded to molecular scaffold, and wherein the methods comprise a multivalent ligand having the structure as formulated as in claim 144.

Whitesides et al., teach methods for inducing a biological response using multivalent ligands, including ligands where the signal recognition element is a peptide, as presented above in the maintained rejection under 35 USC 102(b).

Whitesides et al. does not teach methods comprising a multivalent ligand having the structure as formulated as in claim 144.

Arimoto et al., teach methods for inducing a biological response by multivalent ligands having the structure as formulated as in claim 144, as presented above in the maintained rejection under 35 USC 102(b).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to combine methods of comprising inducing biological response by multivalent ligands that bind to receptors, with methods comprising a multivalent ligand having the structure as formulated as in claim 144.

One of ordinary skill in the art would have been motivated to use methods comprising multivalent ligands of the formula of claim 144, because ROMP methods were applicable to synthesis of multivalent ligands having oligopeptides, as taught by Arimoto et al. at p. 1361, para 3. One of ordinary skill in the art would have had a reasonable expectation of success, because multivalent ligands of the formula of claim 144 were known in the art of targeting receptors.

16. Claims 66, 84, and 150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO 98/46270 (reference 4, IDS filed 10/10/2002), Arimoto et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11) as applied to claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90-92, 94, 95, 140-143, 144, 148, 149, 151, 154, 155, 157 above, and further in view of Painter et al., Journal of Cell Biology, 1987, vol. 105, pp. 2959-2971 (previously cited by examiner).

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal

recognition elements are bonded to molecular scaffold, and wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide, as in claims 66, 84 and 150.

Whitesides et al., teach methods for inducing a biological response using multivalent ligands, including ligands where the signal recognition element is a peptide, as presented above.

Arimoto et al., teach methods for inducing a biological response by multivalent ligands having the structure as formulated as in claim 144, as presented above.

Neither of Whitesides et al. or Arimoto et al., as above, teach methods for inducing a biological response by multivalent ligands, wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide.

Painter et al., teach a derivatized peptide that is an N-formylated peptide that is a ligand that binds to a glycoprotein receptor and acts as a recognition element to stimulate chemotaxis of human neutrophils.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to combine methods of comprising inducing biological response by multivalent ligands that bind to receptors, wherein such methods comprise ligands with derivatized or N-formylated peptides.

One of ordinary skill in the art would have been motivated to use methods comprising derivatized or N-formylated peptides in multivalent ligands in order to stimulate chemotaxis of human neutrophils, as taught by Painter et al. One of ordinary skill in the art would have had a reasonable expectation of success, because N-

formylation of peptides was long known in the art, as was the formylated peptide induction of neutrophil chemotaxis.

17. Claims 91 and 144 are further rejected under 35 U.S.C. 103(a) as being unpatentable over **Whitesides et al.**, WO 98/46270 (reference 4, IDS filed 10/10/2002), **Arimoto et al.**, Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11) as applied to claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90-92, 94, 95, 140-143, 144, 148, 149, 151, 154, 155, 157 above, and further in view of **Truett**, US 6,437,119 B1.

Claims 91 and 144 are drawn to the methods wherein the multivalent ligand has the structure formulated in claim 91, and where there can be two different signal recognition elements, if **m** is not 0 and **n** is not 0.

Whitesides et al., teach methods for inducing a biological response using multivalent ligands, including the structure formulated in claim 91, where **m** is 0 and **n** is 2 or more, as presented above.

Arimoto et al., teach methods for inducing a biological response or three by multivalent ligands, where the ligands are a plurality of vancomycin residues, as presented above.

Neither of Whitesides et al. or Arimoto et al., as above, teach methods for inducing a biological response by multivalent ligands, where there are two different signal recognition elements (i.e., where **m** is not 0 and **n** is not 0).

Truett, US 6,437,119 B1, throughout the patent and, for example, at col. 1, teaches forming a single composition from two or three antibiotics, including vancomycin, in order to attack a bacterial infective agent with different agents simultaneously, and to lessen the development of resistant strains.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to combine methods of comprising inducing biological response by multivalent ligands that bind to receptors, where there are two different signal recognition elements.

One of ordinary skill in the art would have been motivated to use methods where there are two different signal recognition elements in order to attack a bacterial infective agent with different agents simultaneously, and to lessen the development of resistant strains, as taught by Truett. One of ordinary skill in the art would have had a reasonable expectation of success, because Arimoto teaches multivalent ligands with a plurality of vancomycin residues, and Truett teach adding other antibiotics, such as beta lactams, to form multivalent ligands comprising vancomycin and beta lactams.

18. Claims 1-3, 17, 28, 29, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90, 91, 142, 144, 152, **153** and 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kanai et al.**, J. Am. Chem. Soc, 1997, Vol. 119 (41), pp. 1361-1362, (IDS filed 10/10/2002, ref. 45) and **Kaplan et al.**, J. Immunol. Methods 20: (1997) 15-24, (IDS filed 10/10/2002, reference 46).

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal recognition elements are bonded to molecular scaffold, and wherein an intracellular signal, which is released during the biological response, is calcium, and wherein the intracellular signal is a mitogenic signal, as in claim 153.

Kanai et al., throughout the publication, teach methods for inducing interference with erythrocyte agglutination mediated by the carbohydrate-binding protein concanavalin A by introducing multivalent ligands which posses a plurality of saccharide residues, which read on a plurality of signal recognition elements, that are covalently bonded (as in claim 74) to a ROMP-derived scaffold of the formula in claim 82. Kanai, at Table 1, teach more than 100 repeating units in the neoglycopolymer, as in claims 71-73. Kanai et al. teaches at Figure 1, polymers of the general formula of claims 82, 91 (e.g., m=0 and n=2 or more) and 144. Concanavalin A induces an intracellular signal by increasing Ca^{2+} concentration in the cell, as evidenced by Ramaschi et al., (IDS filed 10/10/2002, ref. No. 76).

Kanai et al. does not teach an intracellular signal that is a mitogenic signal.

Kaplan et al., throughout the publication and abstract, and particularly at p. 19, para 2, and p. 22, para 6, teach that concanavalin A acts as a mitogen by binding to the T cell receptor, thereby inducing a cascade of events, including calcium release,

resulting in polyclonal T cell proliferation. Kaplan at p. 15, para 1-p. 16, para 2, teach that T cell activation is an induced physiological process of major importance.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to use methods of inducing biological response by multivalent ligands that bind to receptors, wherein an intracellular signal, which is released during the biological response, is calcium; and wherein the intracellular signal is a mitogenic signal, as in claims 153.

One of ordinary skill in the art would have been motivated to use methods comprising multivalent ligands wherein an intracellular signal, which is released during the biological response, is calcium and wherein the intracellular signal is a mitogenic signal, in order to modulate the important physiological process of T lymphocyte proliferation, as taught by Kaplan et al. One of ordinary skill in the art would have had a reasonable expectation of success, because concanavalin A was long known in the art to induce T cell proliferation, and because Kanai et al. teach the use of multivalent ligands comprising concanavalin A.

Conclusion

19. Claims 1-3, 17-23, 28-30, 41, 42, 59, 60, 62, 64, 66, 68, 71-74, 81-86, 90-92, 94, 95, 140-144, 148-155 and 157 are rejected. Claims 145-147 are allowable over the prior art.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

ms

Continuation of Disposition of Claims: Claims withdrawn from consideration are 4-16,24-27,31-40,43-58,61,63,65,67,69,70,75-80,87-89,93,96-139 and 156.